cancers, ovarian cancers, gastric cancers, colorectal cancers, non-small cell lung cancers, and glioblastomas.

24. (Amended) The method of claim 4 [or claim 19,] wherein said receptor tyrosine kinase is Trk, and said [disease or disorder] cancer or neoplasm is at least one selected from the group consisting of Alzheimer's disease, Parkinson's disease, amyotrophic lateral schlerosis, traumas, nerve injuries, Huntington's chorea, multiple schlerosis, muscular dystrophy, syringomiplia, Tabes Dorsalis, cardiovascular accidents, myasthenia gravis, cervical spondylosis, neurofibromatosis, colorectal cancers and thyroid carcinomas.

REMARKS

Claims 1-4, 10, and 20-25 are pending. Claims 1-4 and 20-24 have been amended. Support for the changes can be found generally in the disclosure, and specifically at page 9, lines 1-13. All of the claims have been rejected under 35 U.S.C. 112 for alleged indefiniteness and lack of enablement . In light of the foregoing claim amendments and remarks to follow, reconsideration and withdrawal of these rejections is respectfully requested.

Indefiniteness

Claim 1

The Examiner first alleges that claim 1 is vague and indefinite in its recitation of a "disease or disorder in an organism characterized by an abnormality in a signal transduction pathway." The Examiner specifically contends that the term "abnormal" is unclear and circular in its meaning and cites page 7, lines 1-3 for that proposition.

The legal standard for indefiniteness is whether a claim read in light of the specification reasonably apprises those of ordinary skill in the art of its scope. Amgen v. Chugai

Pharmaceutical Co., Ltd, 927 F.2d 1200, 18 USPQ2d 1016 (Fed Cir. 1991), cert. denied, 112 S.Ct. 169 (1991).

The Examiner fails to appreciate the specification at page 6, lines 25-29 of the specification in which the term "abnormal" is clearly stated to be "[other] than occurring in the general population of healthy organisms." Thus the meaning *is* clear, and equates roughly with "unhealthy." This is even more clear in light of the Applicants' species election and corresponding claim amendment to reflect cancers and neoplasias.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

The Examiner next requires clarification of what is meant by " 'a' signal transduction pathway". It is respectfully submitted that the amendment inserting "one or more" into the claim renders this rejection moot. Accordingly, reconsideration and withdrawal of this rejection is requested

The Examiner additionally requires clarification of what is meant by "interaction." As noted above, the standard is whether "interaction" as used in the claim reasonably apprises one of ordinary skill in the art viewing the specification of the scope of the claim. It is respectfully submitted that such person would clearly associate "interaction" as used in the claim with "binding." Therefore, reconsideration and withdrawal of this rejection is respectfully requested.

In light of the above, reconsideration and withdrawal of all claim 1 rejections for alleged indefiniteness is requested.

Claim 2

The Examiner contends that claim 2 is vague and indefinite in that "the encompassed diseases or disorders cannot be determined." The legal standard for indefiniteness, again, is

whether a claim read in light of the specification reasonably apprises those of ordinary skill in the art of its scope. One of ordinary skill in the art viewing the specification would consider, e.g., the discussion of pages 15-23 of the specification (section entitled "Targeted Diseases") and clearly arrive at a determination contrary to that of the Examiner.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

The Examiner next contests the term "therapeutic amount" for allegedly not having a "definable functional limitation." If one applies the rule of law espoused in Amgen, however, one arrives at a different conclusion. One of ordinary skill in the art viewing the specification would consider the term clear. For example, the Examiner cites page 8, lines 18-21 of the specification, but neglects the added context provided by reading further to page 9, line 11. If one reads this entire section, the meaning of the term is more than clear. There one finds support for the term "therapeutic" in reference to ameliorating harm, e.g., "discomfort, or decreased life expectancy," and even more detailed discussion is found on page 9, lines 3-11.

Therefore, reconsideration and withdrawal of this rejection is respectfully requested.

The Examiner next contends that "there is no information supplied regarding the characteristics defining an APB recognition region such that a protein having one may be defined." Again, this assertion is contrary to the law above as applied to the detailed discussion beginning, e.g., on page 5, line 19 et seq. of the specification. The APB domain has been identified as part of a known protein, Shc, and thus it is true that such domain *can* readily be identified.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Claim 3

The Examiner contends that claim 3 is indefinite in that "one or more activities" of a receptor tyrosine kinase (RTK) do not provide "a definitive activity of the RTK." It is respectfully submitted that the amendment noted above renders this rejection moot. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Claim 4

It is respectfully submitted that claim 4 as amended renders the rejection of this claim moot. Therefore, reconsideration and withdrawal of this rejection is respectfully requested.

Claim 24

Claim 4, from which claim 24 depends, has been amended to provide antecedent basis for "TRK" in claim 24. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Enablement

The Examiner admits "the specification discloses the discovery of a heretofore unknown binding by a region within the N-terminus of Shc to autophosphorylated EGFR, HER-2, or TrkA," but yet rejects the claims for alleged lack of enablement, stating

> There is insufficient objective evidence provided to support a role for Shc APB binding (or any other APB protein binding) in the mediation of signal transduction or in the onset and development of cancer. There is no objective evidence provided that disruption or promotion of Shc APB binding to EGFR, HER-2, TrkA or any other APB-receptor interactions results in the predictable remediation of symptoms of cancer. No therapeutic agents which disrupt or promote such binding are provided, including any agents which bind to the APB domain. Indeed, the region of the EGFR receptor to which the APB domain of Shcp binds is ***not*** identified. Neither is the role, if any, of the binding in signal transduction provided. *Paper 12, pg. 5.* (emphasis added)

It is respectfully submitted that, by this statement, the Examiner is more concerned with utility than enablement. Specifically, it appears as though the Examiner is incredulous as to whether the use and manipulation of APB domains can treat cancers and neoplasms. However, as the specification demonstrates, the APB domain is a necessary component of an important pathway that is widely implicated in the art with certain cancers. Everyone in the art will therefore appreciate that disruption of this domain or its binding partner will likely also disrupt cancers, and that this relationship can advantageously be used in treatments. The specification makes clear that this can be done using any one or more of numerous established methods.

For example, the specification, specifically on page 29, under the section entitled "III. Identification of APB Modulating or Binding Agents," describes numerous established approaches, mostly in vitro, that can be used to identify such disrupting agents, i.e., antibody targeting, peptide targeting, small molecule inhibitor use, etc. This is discussed in detail through page 37. If the Examiner is alleging an *in vitro/in vivo* distinction or discrepancy, the Examiner is respectfully referred to the Federal Circuit's decisions in In re Brana, 51 Fed. 3rd 1560, 1566 34 USPQ2D 1436, 1441 (Fed. Cir. 1995) (reversing a PTO decision that *in vitro* data did not support *in vivo* applications) and Cross v. Iizuka, 753 Fed. 2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1995) (ruling that an exact in vivo/in vitro correlation is not required).

Utility established, it is further submitted that the Examiner's contention of a lack of enablement is fundamentally at odds with the almost fifty pages of detailed materials provided in the specification, beginning, e.g., on page 16, line 19 and running through page 65, and what this signfies to one of ordinary skill in the art.

The test for enablement is a question of law answered by considering what the specification teaches to one of ordinary skill in the art as of the time of filing. The law provides

that one of ordinary skill in the art viewing the specification must be able to make and use the full scope of the claimed invention without "undue experimentation." In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1991); Amgen, 927 F.2d at 1212. The Federal Circuit, in In re Wands, 858 F.2d 731 (Fed. Cir. 1988), established eight useful factors to be considered. Those factors are considered below. First, however, the specification teachings are discussed.

Pages 16-23 of the specification note the participation of EGFR, HER-2, and TrkA in cancer and neoplasms and the relationship of the Shc adapter protein in the process and how this can be usefully exploited. For EGFR, e.g., the specification beginning on page 17, line 6 states that there are several ways of assaying for altered EGFR, including measuring autophosphorylation of an EGFR substrate, activation of an adapter molecule, and/or measuring increased cell division. The specification further statess that these activities can be measured using techniques known in the art, e.g., using autophosphorylation measured by anti-phosphotyrosine antibodies, and increased cell division monitored by measuring tritiated thymidine incorporation into DNA.

Similarly, on page 18, lines 23 et seq. is discussion of how HER-2 activity can be assayed using the invention. The very same assays noted above can be applied here, as well as for Trk receptor tyrosine kinase.

On page 23, line 26 is a heading entitled "Therapeutic Agents," which are said to include organic molecules and polypeptides which bind to the APB domain or APB region site. For polypeptides, it is further stated,

> Therapeutic...polypeptide agents can be designed to bind to an APB domain or a APB recognition region. Polypeptides binding to an APB recognition region preferably are at least ten amino acids in length *and contain the amino acid sequence asparagine-proline-x-(phosphorylated) tyrosine, where x refers to any amino acid.* Specification, pg. 23 (emphasis added)

This particular statement is important because it directly contradicts the Examiner's statement on page 5 of paper 12: "Indeed, the region of the EGFR receptor to which the APB domain of Shc binds is not identified." In light of the emphasized portion of the foregoing statement of the specification, this is simply not true.

Continuing on at page 26, line 5 is a section in the application entitled "Antibodies Able to Modulate APB Mediated Activity." Citations and discussion are provided therein that allow one of skill in the art to synthesize antibodies having *in vitro* and *in vivo* activity against APB-domain bearing proteins. See, e.g., page 27, lines 8 through page 29, line 14.

And beginning on page 29, line 16 is a section entitled "Identification of APB Modulating or Binding Agents." It is submitted that this section is highly probative of enablement and directly refutes the Examiner's contentions. This section describes affinity binding methods wherein an APB domain containing protein is exposed to various potential binding agents and those showing binding affinity isolated and characterized according to routine methods in the art:

> Molecules exhibiting binding activity may be further screened for an ability to effect APB binding or modulate APB mediated activity. For example, the molecule can be tested for its ability to increase or decrease APB binding. Alternatively, the molecule may be tested for its ability to increase or decrease one or more activities mediated by the APB domain protein.
> Specification, pg. 31, lines 3-9.

The specification continues with discussion of alternative assays that can be used to identify compounds that can be used in methods of the invention. Such assays include *in vitro* complex formation (page 31, line 12) and co-immunoprecipitation techniques well known to those of ordinary skill in the art (page 31, lines 24-25). Further helpful details are found on page

32, lines 7 et seq. wherein are described detailed methodologies that may be employed with the invention to confirm that the invention is enabled.

Because the methods of the invention can take many forms including using therapeutic peptides, there is further discussion, beginning page 34 and again on page 52, of gene therapy techniques that can be employed using peptides that display activity against APB domain containing proteins.

Beginning on page 44, line 16 is a further section entitled "Diagnosis." This section continues through line 5 of page 46 and describes how protein complexes involving APB binding may be utilized in the prognostic evaluation of the condition of a patient suspected of exhibiting an APB affiliated signal transduction disorder.

On page 46, line 7 is a section entitled "Administration." That section describes how agents that modulate APB activity can be administered to a patient using standard techniques such as determining the LD_{50} and the ED_{50}. Page 47, line 17 et seq. describes how one of skill in the art possessed with knowledge such as found in Fingl et al. (1975) "The Pharmacological Basis of Therapeutics," Chapter 1, can put to use the invention for treatment. And, again, on page 48, line 11 is stated that resort may be had to "Remington's Pharmaceutical Sciences," 1990, 18th ed. Mack Publishing Co., Easton, PA, for various routes and modes of administration. See, e.g., page 52, line 8. Remington's is an extremely thorough and well-respected treatise on pharmaceutical formulations.

The Examiner's contention of nonenablement is further undermined by the example given on page 53 of the specification. Even as noted by the Examiner in Paper 12, page 5, working examples such as this are probative of enablement under governing patent law. In re Wands, 858 Fed.2d 731, 8 USPQ2D 1400 (Fed. Cir. 1988).

The example in this case shows how Shc is ubiquitously expressed and displays Src homology and can transform fibroblasts and differentiate PC12 cells in a RAS-dependent fashion. The example further notes the cloning of two receptor targets including Grb2 and Grb7, each of which possesses SH2-type domains and can bind tyrosine-phosphorylated growth factor receptors and tyrosine-phosphorylated cytoplasmic proteins. Page 55, lines 7-21. In addition, and as further support, at least a half dozen citations are provided in the application to support this contention.

And under the same example, page 56, line 23 of the specification,

> Shc appears to interact with tyrosine-phosphorylated proteins bearing the sequence, Asn-Pro-X-Tyr (P). This interaction is unusual for SH2 domains that usually select specificity based on amino acids carboxyl-terminal to the phosphotyrosine...in this report we demonstrate that Shc has a second domain in its amino terminus, distinct from the SH2 domain, that can interact with tyrosine-phosphorylated growth factor receptors. The data suggest a novel mechanism whereby signaling molecules can interact with growth factor receptors.
>
> Our results reveal a novel growth factor receptor binding domain in the amino terminus of Shc...This result appears to reveal a new mechanism whereby proteins can interact with growth factor receptors and other tyrosine-phosphorylated proteins.

The Examiner has cited In re Wands in support of the rejection and the factors cited therein including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. However, even a cursory analysis of these factors as applied to the fifty plus pages of specification just discussed clearly suggests otherwise. An analysis of the Wands factors follows.

Quantity of Experimentation Necessary/Amount of Detection or Guidance Presented

A patent need not teach and preferably omits what is well known in the art. In re Buchner, 929 Fed. 2d 660, 661, 18 USPQ2D 1331, 1332 (Fed. Cir. 1991). The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (International Trade Commission 1983), *aff'd sub. nom.* The test of enablement is not whether any experimentation is necessary but whether, if experimentation is necessary, it is undue. In re Angstadt, 537 Fed. 2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Further, "an extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 561 Fed. 2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 Fed.2d at 737, 8USPQ2D at 1404 (citing In re Angstadt, 537 Fed.2d at 502-504, 190 USPQ at 217-219. Time and expense are merely factors in the consideration and not controlling factors. United States v. Telectronics, Inc. 857 Fed.2d 778, 785, 8 USPQ 2d 1217, 1223 (Fed. Cir. 1988), cert. denied 490 US 1046 (1989).

The Examiner noted none of this, and it is respectfully submitted that the details of the specification comport well with this exposition of the law. As noted, over fifty pages of detailed guidance are provided in the specification.

Accordingly, it is respectfully submitted that these factors inure to the Applicants' favor.

The Presence or Absence of Working Examples

As noted, a working example is provided on page 53 of the instant specification. The example discloses how Shc ubiquitously expresses Src-2 homology and can transform fibroblasts and differentiate PC12 in an independent fashion, and how Shc binds a variety of tyrosine-phosphorylated growth factor receptors. The example also describes the cloning of the Shc fragment and the binding of the corresponding expressed product to the amino terminal domain of the autophosphorylated EGF receptor, as well as the HER-2/Neu and TrkA receptors. Given these specific interactions, the Examiner's position that no guidance or direction is provided to enable the invention is untenable-- especially given that a working example as described is provided.

Accordingly, it is respectfully submitted that this factor inures to the Applicants' favor.

The Nature of the Invention

The invention concerns a domain in the amino terminus of Shc that is implicated in tyrosine kinase-mediated signal transduction. The domain is distinct from the Sh2 domain and represents a newly elucidated mechanism of protein interaction with growth factor receptors and other tyrosine-phosphorylated proteins. This amino terminal domain is shown to cooperate with the Sh2 domain to promote binding to growth factor receptors. The nature of the invention thus has importance in signal transduction, particularly tyrosine kinase systems, and specifically in modulating signal transduction of such systems. This is clear, and can be exploited as claimed using methodologies well known in the art.

Accordingly, it is respectfully submitted that this factor inures to the Applicants' favor.

The State of the Prior Art and the Relative Skill of Those in the Art

Literally dozens of citations are provided in the specification that demonstrate how signal transduction is implicated in cancer and neoplasms. These citations discuss, for example, EGFR, Neu, and Trk phosphotyrosine kinase systems. Using such references, the APB domain described by the Applicants may be used advantageously and in unprecedented fashion to modify these systems in order to thwart or ameliorate disorders characterized thereby, namely cancer and neoplasms.

In addition to the specific references provided on signal transduction, more generic, comprehensive literature is also provided to enable pharmaceutical formulations based on molecules found to interact with the APB binding domain and corresponding binding partner. For example, hybridoma technology is cited on page 27 as one example of how to produce targeting molecules. Also, "Remington's Pharmaceutical Science" is mentioned on page 48, lines 13-15. This seminal source provides excellent guidance to one of ordinary skill in the art wishing to practice the invention.

In light of the wealth of citations and guidance already provided in the specification, it is not even necessary that one of ordinary skill in the art have a high skill and knowledge level to practice the invention.

Accordingly, it is respectfully submitted that these factors inure to the Applicants' favor.

Predictability or Unpredictability of the Art

Given the numerous citations and quantity and quality of discussion provided in the specification, the art is submitted to be predictable. However, even if it were unpredictable as the Examiner contends, applicable law governing enablement requires that the Examiner consider *all* the evidence related to each of the factors, and render a conclusion based only on the

evidence *as a whole.* In re Wands, 858 Fed.2d at 737, 740 8 USPQ2D at 1404, 1407. Moreover, the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art, as well as the predictability in the art. In re Fisher, 427 Fed. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Even if the fifty pages of specification guidance discussed above could somehow be deemed not enabling or otherwise insufficient, the amount or knowledge in the state of the art and the predictability in the art are sufficiently great as to negate such contention.

Accordingly, it is respectfully submitted that this factor inures to the Applicants' favor.

The Breadth of the Claims

The claims are tailored to comport with the amount of specification guidance and knowledge level in the art. Such high combined level of skill and disclosure suggests that the claimed invention is enabled.

Accordingly, it is respectfully submitted that this factor inures to the Applicants' favor.

Alleged Admissions in the Specification

The Examiner makes issue of certain statements in the specification, contending that they demonstrate that the claimed invention is not enabled. However, a closer examination of these statements suggests otherwise. These passages must be read in their proper context and analyzed as a *whole,* as the Wands decision requires.

Moreover, it is not necessary to know exactly how the invention works as long as utility is demonstrated and described sufficiently to put the invention to use; what matters is that one of ordinary skill in the art reading the specification can, to a reasonable certainty, put the invention to use without undue experimentation.

The Examiner Has Not Met Its Burden

In order to make a rejection based on enablement, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 Fed. 2d 1557, 1562, 27 USPQ2D 1510, 1513 (Fed. Cir. 1993). It is respectfully submitted that the Examiner has not met this burden. Even if such were the case, it is submitted that the Applicants herein have described sufficient evidence to rebut the Examiner's contentions.

CONCLUSION

In view of the amendments and discussion above, the Applicants respecfully submit that the claims are in condition for allowance and respectfully request a notice to that effect.

A petition and fee or a two month extension of time is enclosed herewith. If inadequate, please charge Deposit Account 50-1273 for the correct amount.

Respectfully submitted,

BROBECK, PHLEGER & HARRISON LLP

Dated: 6/20/00 By: S/

Edward O. Kreusser
Reg. No. 38,523

BROBECK, PHLEGER & HARRISON LLP
12390 El Camino Real
San Diego, California 92130
Telephone: (858) 720-2500
Facsimile: (858) 720-2555